Author’s response to reviews

Title: Employment of an Algorithm of Care Including Chest Physiotherapy Results in Reduced Hospitalizations and Stability of Lung Function in Bronchiectasis

Authors:

Jordan Powner (jpowner@uabmc.edu)
Andrew NeSmith (anesmith@uab.edu)
Denay Kirkpatrick (dpkirkpatrick@uabmc.edu)
Jessica Nichols (jknichols@uabmc.edu)
Brent Bermingham (bbermingham@uabmc.edu)
George Solomon (gsolomon@uabmc.edu)

Version: 2 Date: 08 Mar 2019

Author’s response to reviews:

Dear Associate Editor and Reviewers,

Thank you for the opportunity to submit a revised version of our manuscript entitled “Chest Physiotherapy as Part of an Algorithm of Care Results in Reduced Hospitalizations and Stability of Lung Function in Bronchiectasis”. We have substantially revised the manuscript to reflect the response to the reviewers. In addition, we offer a point-by-point response to the reviewers below with responses in blue typeface.

Thank you for considering our revised work.

Sincerely yours,

George M. Solomon, MD-Corresponding Author

Assistant Professor of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine
Associate Scientist Gregory Fleming James Cystic Fibrosis Center
Director of UAB PCD and Non-CF Bronchiectasis Program
Director of the Center for CFTR Detection
University of Alabama Birmingham
Reviewer reports:

Michal Shteinberg (Reviewer 1):

Thank you to the reviewer for this careful review of our manuscript.

General: This is a retrospective review of 43 newly diagnosed or newly referred patients with bronchiectasis who were offered a "bundle" of recommended care. This bundle included chest physiotherapy with high frequency chest wall oscillations (HFCWO), hypertonic saline for 95% of patients, macrolide antibiotics (35%) and inhaled antibiotics where appropriate. The authors show that these patients have a reduction in exacerbations when on treatment compared to the preceding year. While this study emphasizes the importance and benefit of good care in bronchiectasis, the findings are not new, and were described in a larger scale, multicenter study (Chalmers et al., Am J Respir Crit Care Med. 2018)

Thank you for pointing this out. Our study was aimed at the outcomes of our cohort of bronchiectasis patients who were treated with an algorithm of care that includes adding High Frequency Chest Wall Oscillation (HFCWO). The manuscript published by Chalmers AJRCCM June 2018 demonstrated factors surrounding exacerbations whether there existed a frequent exacerbator phenotype in Bronchiectasis. The paper did conclude that the use of prophylactic antibiotics reduced exacerbations and that only a limited number of Bronchiectasis patients were on known beneficial treatments. The trial also concluded that larger randomized clinical trials were needed for treatments to better understand their full effects long-term. HFCWO therapy was not reviewed in this manuscript. As this work was published as we were concluding our work, it was not originally included in our discussion, but its findings have been included now.

Major:

The authors focus on HFCWO, and present the study objective as looking at this intervention (the title and last two paragraphs of the "introduction"). However, as a "bundle" of care was introduced, the effects of HFCWO cannot be isolated. The reduction in exacerbations may have resulted from the other interventions- inhaled hypertonic saline, macrolides- both proven to effectively reduce exacerbations. The manuscript should focus on showing that the treatment algorithm as a whole, not just airway clearance, is effective in reducing severe exacerbations.

We agree and do not intend to assert the conclusion that HFCWO was the only effective part of the treatment algorithm. The wording was changed throughout the manuscript to reflect that the treatment algorithm produced these results and not just HFCWO. The background in the abstract and beginning of the manuscript underwent the most editing to reflect this change. HFCWO was still emphasized as an integral part of the treatment algorithm considering its novel use in a long-term study.

Minor:
1. Non-CF bronchiectasis should be replaced by "bronchiectasis" - see review by Chalmers, Elborn.

Non-CF Bronchiectasis or NCFBE was replaced throughout the manuscript and exchanged with Bronchiectasis.

2. Table 1: what is "usual care?"

Usual care was defined in text surrounding Table 1. Throughout this manuscript “usual care” involved nebulized bronchodilators and mucolytics with as needed antibiotics.

3. Page 8, line 41: "The patients that met criteria:" should be "the patients who met criteria"

Thank you for pointing this out. This wording was changed.

4. Page 10, line 46: "Despite greater than 45% of the patient's not requiring hospitalization pre-algorithm or post-algorithm…" - unclear sentence.

This sentence was rephrased to clarify that despite a significant number of patients not requiring hospitalization either pre or post treatment with the study’s algorithm there was a still a significant reduction in the number of hospitalizations during treatment with the algorithm.

5. Table 2: please include etiology of bronchiectasis. Were there patients with PCD? COPD? NTM?

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Table 2 was not updated with the cause of their bronchiectasis as that was not emphasized when recruiting the patients into the study. We recruited based on a diagnosis of Bronchiectasis and the on the cause of said disease. Many of the patients have “idiopathic bronchiectasis” after evaluation by the diagnostic testing algorithm outlined by by Mcshane PJ AJRCCM 2013.

Annemarie Lee (Reviewer 2): The aim of this retrospective study is to identify the effects of high frequency chest wall oscillation, bronchodilator and mucolytic therapy in addition to antibiotic therapy in lung function and rate of hospitalisations in people with bronchiectasis. The study overall demonstrates some interesting date, but there are key points which need further clarity.

Thank you to the reviewer for the careful review and excellent suggested edits. We offer a point-by-point response below
Abstract:

The chest physiotherapy component of the study is considered the key contributor to the outcomes of interest. However, this was provided as part of a treatment algorithm, which includes bronchodilator therapy for 100% of patients and mucolytic therapy for 95%. It is misleading to the readers to attribute the findings to a single component of the treatment algorithm and this needs to be modified throughout the manuscript. This is particularly important given the % of patients commenced on bronchodilator and mucolytic therapy as part of the algorithm and this therapy was started before airway clearance.

In view of this, the background statement needs to be modified to accurately reflect what was studied.

The term NCFBE has been recommended to be changed to simply bronchiectasis, in reference to this being a diagnosis/disease in its own right and worthy of this change (refer to 'Reclaiming the name 'bronchiectasis', Thorax 2015). Please modify through the manuscript.

Reviewer 1 also raised these concerns, and changes have been made throughout the manuscript to reflect these shared concerns.

Background

The authors have referred to predominantly CF guidelines/papers in mucociliary clearance therapy, but there are at least 2 Cochrane reviews focused on bronchiectasis, which have specifically reviewed the literature in this population and provide an overview what was techniques have been studied.

The Cochrane reviews were not included in the write up because of the low number of clinical trials that the components of the algorithm have undergone. The studies referenced were ones that included similar endpoints as the one in our study and also that included when publishing guidelines from different authorities. The pertinent individual studies have been referenced throughout the manuscript as well as the most recent Cochrane review.

Line 45 - techniques of huffing and coughing or autogenic drainage are classed as expiratory flow therapies rather than mechanical therapies (Polverino et al 2017).

We agree with this suggestion. Active cycling breathing with huff coughing has been reclassified in the paper as expiratory techniques.

Line 50, what other inhaled medications are the authors referring to if not, rhDNase or hypertonic saline? Could this be spelt out more clearly (ie. Bronchodilator, corticosteroid therapy?)
A comma has been deleted so that no other inhaled medications besides inhaled hypertonic saline and DNAase are being referred to, as no other inhaled medications were used in our study.

The authors highlight that the primary endpoint of the study was to determine the clinical effectiveness of a treatment algorithm centred on early initiation of HFCWO as an airway clearance therapy, but there are multiple confounders in the outcomes selected.

Thank you for raising this concern that was shared by Reviewer 1. The manuscript was changed to reflect that clarify our findings that the algorithm as a whole was responsible for the results and that the specific components could not be isolated as the reason for the conclusions.

Methods

How was the diagnosis of bronchiectasis confirmed for the database? (HRCT)

Diagnosis was based on HRCT images and clinical symptoms. The diagnosis and work up of bronchiectasis was based off the work of Mcshane PJ AJRCCM 2013.

What symptoms were considered to warrant entry by clinic staff?

Symptoms included chronic cough or sputum production along with dyspnea.

Was the definition of an exacerbation based on previous references?

The consensus definition of a Bronchiectasis exacerbation by Hill AT, ERJ 2017 was inserted in the manuscript. All our exacerbations were based off this definition.

It is stated in Table 2 that 95% of patients were commenced on HTs - does this mean that the remaining 5% were commenced on n-acetylcysteine inhaled therapy?

Yes. Table 2 was changed to reflect this.

In the methods, it is stated that HFCWO therapy was offered to augment therapy, but the primary aim was stated that this therapy was the centre of the study and that other treatments (macrolide and nebulised mucolytics) were adjunctive therapy?

No, all were components of the algorithm. HFCWO is a novel research topic in Bronchiectasis and so was given special consideration since the other components are proven treatments with long term clinical trials.

The word 65 should be written in full

All numbers that were not a single digit, part of a table, or in a figure figure have been written out.
What was the compliance/adherence rate to each of the types of therapies over the follow up period? This is particularly important for mucolytic and airway clearance therapy and it has been previously documented that adherence in adults with bronchiectasis is troublesome. Without adherence rates, it is difficult to be clear on the conclusions of the study, particularly with multiple treatments.

This is a weakness of the study. Given the outpatient nature of the study and that some of the components were mechanical there is no current method to quantify adherence rates besides surveying the patient in clinic. Planned followup studies will employ new means to capture adherence through next generation devices that allow for data capture.

Results

For all hospital records of exacerbations, can it be guaranteed that all data related to this outcome was captured by the database? If not, it should be acknowledged as a limitation of the study.

Complete hospital records were obtained for thirty nine of the patients involved and these records were included in our analysis.

What defines a severe exacerbation?

We defined a severe exacerbation as a hospitalization or need for outpatient intravenous antibiotics. The definition and need for therapies was based on the work by Chalmers JD AJRCCM 2014.

The following sentences 'Thus, allowing an estimation of the effect the algorithm had on the amount of antibiotics prescribed and the number of severe exacerbations….' And "although a small subset of participants did have an increased severe exacerbation rate…" are poorly phrased, please rephrase.

These sentences were rephrased in the manuscript

Add 's' on end of purposes

“S” was added.

According to what reference/clinical guideline is a course of home antibiotics considered a severe exacerbation? Is there a precedence for this?

A course of home intravenous antibiotics was considered a severe exacerbation, but not oral antibiotics.

The authors switch between participants and patients. It is best to select one and be consistent throughout.
We agree. The word participants was dropped from the manuscript and the word patients was used exclusively.

Discussion

The first paragraph of the discussion includes some information which would be better placed in the background section. The authors need to consider also the Australian and New Zealand guidelines for bronchiectasis, as these directly comment on airway clearance therapy.

A sentence was included to mention the Australian and New Zealand guidelines which also do not mention HFCWO.

The American guidelines are incorrectly attributed to the American Thoracic society and these are not originating from this society, and are not guidelines, but a clinical review. This was addressed and reference as a clinical review and another clinical review was added from the same journal.

The authors conclusion that HFCWO can be a beneficial long term treatment is only true in the context of the other treatments that participants were exposed to as part of the study. With 95% of patients receiving mucolytic therapy, which has been proven to impact on lung function and exacerbation rates, the results found cannot be directly attributed to one treatment (or giving most of the credit to that one treatment). This needs to be modified through the discussion.

The discussion was further modified to include the point that the treatment algorithm as whole result in the clinical outcomes detailed; these are not attributable to HCFWO alone.

The authors mention frequent exacerbators in relation to macrolide therapy - were there any frequent exacerbators in the current study?

Yes, patients that were considered the frequent exacerbator phenotype were included in this study. This was based off Chalmers Am J Respir Crit Care Med June 2018. Multiple patients had more than 2 exacerbations per year according to the data pre and post treatment with the algorithm.

The authors mention other comorbidities, but they have only eluded to COPD, which other comorbidities did participants have in this study to justify this statement?

We did not exclude or include based on their morbidities. The only comorbidities that we tracked or mentioned was concurrent pseudomonas infection and chronic obstructive disease. Given our mean age was 67 our patient population that was involved had other comorbidities including: rheumatological diseases hypertension, and chronic kidney disease.

Other weaknesses include the lack of detail regarding compliance to treatment and the fact that being in a database and attending clinic regularly for follow up may have influenced some outcomes.
We agree assessing compliance was limited to subjective measurement alone in this study.

In addition there may have been an effect of regular clinic visits and being enrolled in a database on our outcomes. These limitations have been acknowledged in the revised conclusions section.

The conclusion has some repetitive points particularly around limitations of the study.

The conclusion was edited to help prevent some the repetitive nature.

Figure 1 - it is difficult to identify the mean lines in these figures.

The figure was altered to improve visualization of the mean lines.

Figure 2 - the shading in figure 2B, needs to be clearer, it is difficult to interpret.

The color of the shading was changed to make it easier to interpret.